A rapid access to the core skeleton of atypical tricyclic polyprenylated acylphloroglucinols

Blanca Tolon,[a,b] Bernard Delpech,[b,*] and Christian Marazano[b,†]

[a]*Center of Pharmaceutical Chemistry, Calle 200, esq. 21, Atabey, 16042, Havana City, Cuba*
[b]*Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles CNRS,*
Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
E-mail: bernard.delpech@icsn.cnrs-gif.fr

Dedicated to the memory of Christian Marazano
[†] **Deceased on November 12th 2008**

Abstract

A synthesis of ($4S^*,6S^*$)-2,4,6-triallyl-3,3-dimethylcyclohexanones, and the treatment of their TMS enol ethers with malonyl dichloride in the presence of $BF_3 \bullet Et_2O$, are reported. Formation of a ketoacid, resulting from acylation without cyclization, and of a tricyclic phloroglucinol derivative, involving Effenberger annulation with concomitant *O*-cyclization, were obtained. The tricyclic compound has the core skeleton of the hyperibones H and I, atypical natural polycyclic polyprenylated acylphloroglucinols. Mechanistic and stereochemical aspects are discussed.

Keywords: Polycyclic polyprenylated acylphloroglucinols (PPAPs), silyl enol ethers acylation, Effenberger annulation, malonyl dichloride, bicyclo[3.3.1]nonane-2,4,9-triones

Introduction

More than one hundred polycyclic polyprenylated acylphloroglucinols (PPAPs) with a bicyclo[3.3.1]nonane-2,4,9-trione core skeleton have been isolated from plants and trees of the family Clusiaceae (Guttiferae), some of them presenting interesting biological activities.[1] These compounds can be divided principally into two classes, with type A possessing a bridgehead acyl group adjacent to a quaternary center, and type B having two bridgehead isoprenyl chains and an acyl group bound to C-3.[2] Moreover, irrespective of the type (A or B), some PPAPs have the 7-substituent either in an equatorial *exo* position (i.e., nemorosone,[2] clusianone,[3] or aristophenone[4]) or in an axial *endo* position (i.e., 7-*epi*-nemorosone[5] or xanthochymol[6]). Finally, natural products with a tricyclic core, with an oxygen heterocycle, are also found as in the case of garsubellin A[7] or of hyperibone I[8] with their 4-oxa-tricyclo[6.3.1.0[1,5]]dodec-5-ene-7,12-dione skeletons.
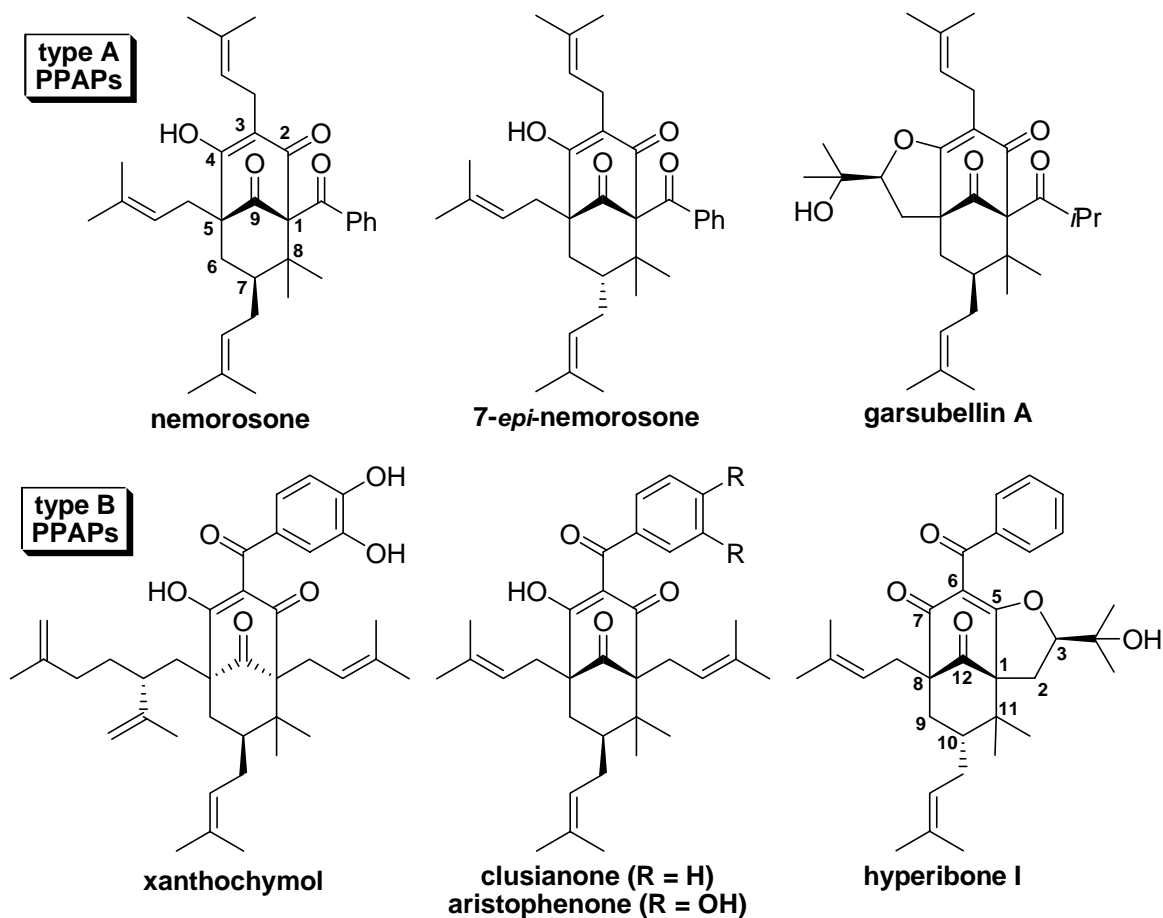
The first total syntheses of a PPAP were those of garsubellin A (type A).[9] Syntheses of clusianone (type B) were subsequently reported by several groups[10] including ours.[11] Nemorosone also has been the subject of a total synthesis.[10e] Our interest in the field of PPAPs came from the observation that xanthochymol was active in a tubulin disassembly inhibition test.[6] After our work leading to the isolation of oblongifolins A—D,[12] we undertook synthetic studies toward type B PPAPs.[11, 13]

We previously showed that the boron trifluoride catalyzed Effenberger α,α'-annulation[14] of isomeric 2,4,6-triprenyl-3,3-dimethylcyclohexanones TMS enol ethers **1** with malonyl dichloride allowed the formation of the bicyclo[3.3.1]nonane-2,4,9-trione **2** with an equatorial prenyl group.[11] This led to a short synthesis of (±)-clusianone via *C*-benzoylation of the enolic β-dicarbonyl moiety of **2** (Scheme 1). We also observed the formation of interesting secondary products possessing an additional tetrahydropyran ring, owing to the cyclization of a prenyl group with the oxygen of an enol moiety.[11]
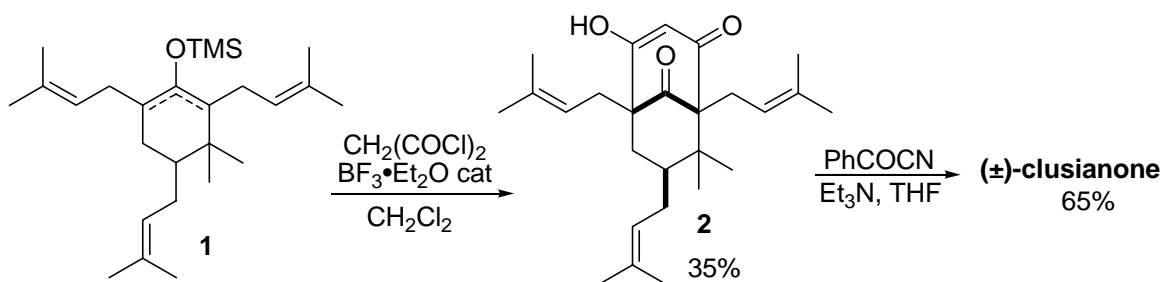
Scheme 1. Synthesis of (±)-clusianone via Effenberger annulation.

Following up on this observation, we wanted to examine the Effenberger annulation reaction with a compound such as **1**, but with allyl groups instead of the prenyl chains, in order to minimize undesired cyclizations. Accordingly, we report here our work concerning the preparation of (4S*,6S*)-2,4,6-triallyl-3,3-dimethylcyclohexanones and the reaction of their TMS enol ethers in BF$_3$•Et$_2$O catalyzed Effenberger annulation conditions.

Results and Discussion

Preparation of (4S*,6S*)-2,4,6-triallyl-3,3-dimethylcyclohexanones 8
The synthesis of the epimeric pentasubstituted ketones **8** was achieved, according to Scheme 2, the two first steps requiring no purification.
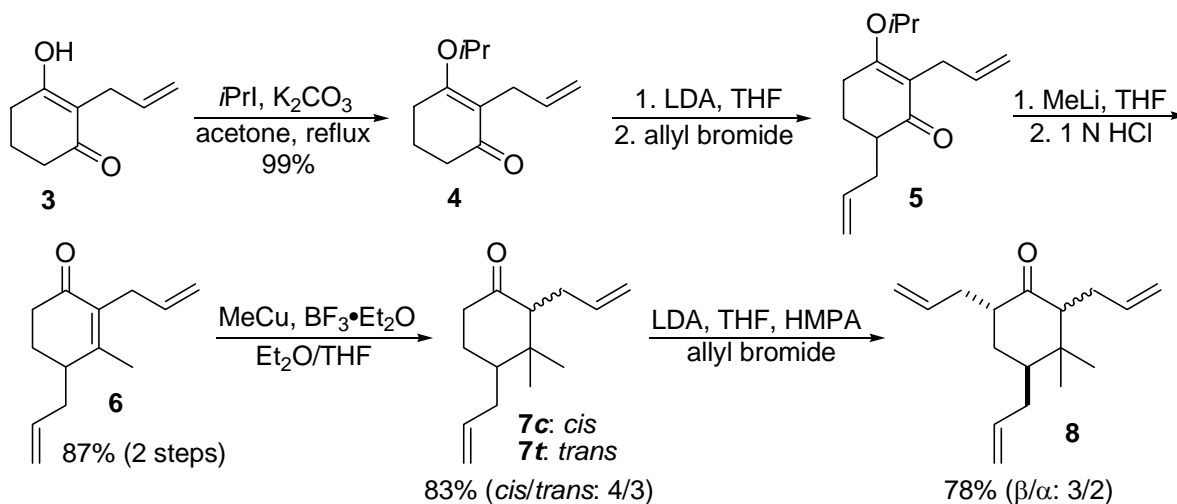

Scheme 2. Synthesis of 2,4,6-triallyl-3,3-dimethylcyclohexanones **8**.

Starting from the known 2-allylcyclohexane-1,3-dione **3**,[15] O-alkylation with isopropyl iodide[16] led to the vinylogous ester **4**. Stork-Danheiser kinetic allylation[17] of **4** followed by methyllithium addition and acidic hydrolysis afforded enone **6** with 87% yield. BF$_3$•Et$_2$O

promoted conjugate addition of methylcopper[18] allowed the formation of the *gem*-dimethyl ketones **7** as a mixture of *cis* and *trans* isomers. The suitably substituted cyclohexanones **8** were obtained, by regio- and stereoselective allylation in the presence of HMPA (axial attack on the less substituted enolate distal from the *gem*-dimethyl).

Formation of TMS enol ethers 9 and their reaction with malonyl chloride

Silyl enol ethers **9** were formed, with TMSOTf in the presence of triethylamine, and obtained as a mixture of three regio- and stereoisomers, the major products having probably the enolic double bond remote from the *gem*-dimethyl.[19] This mixture was used without purification for the annulation step (Scheme 3). We first tested **9** under best conditions we developed for the formation of the bicyclo[3.3.1]nonane-2,4,9-trione **2** (one equivalent of malonyl dichloride in the presence of 0.3 equivalent of BF$_3$•Et$_2$O, from -10 °C to rt).[11] Final treatment with DMAP, which was used initially in the TMSOTf catalyzed reaction in order to facilitate silyl enol ether reformation and acylation, and also to trap acidic species, was kept with this boron trifluoride variant.[11]
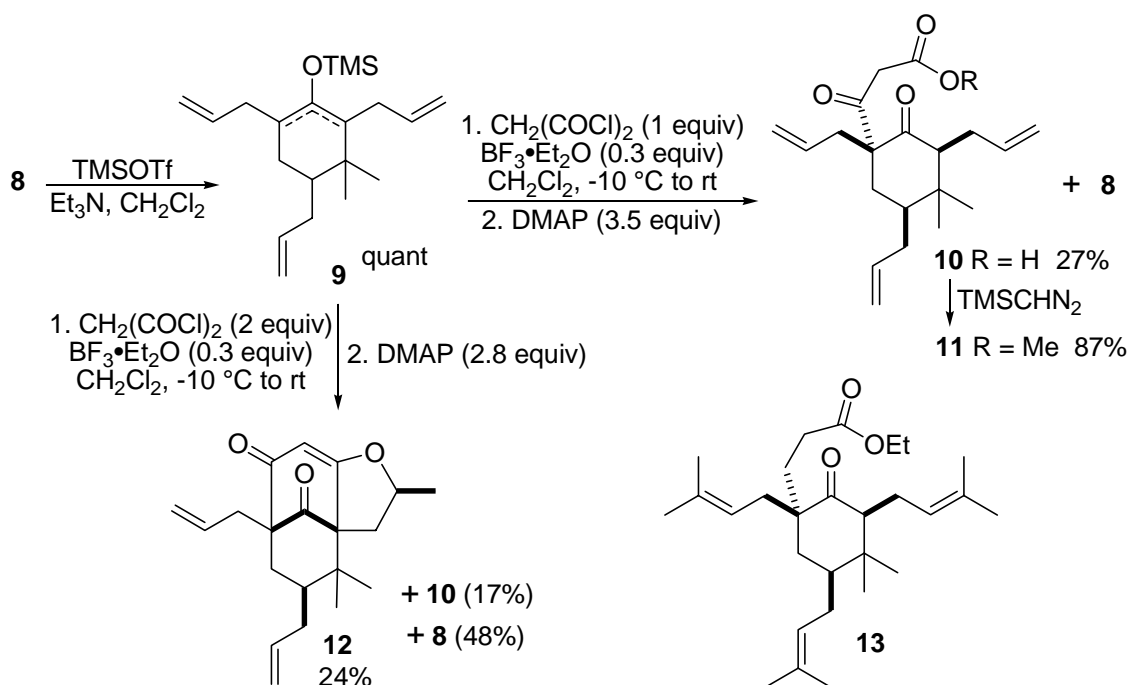
Scheme 3. Reaction of TMS enol ethers **9** with malonyl dichloride in the presence of BF$_3$•Et$_2$O.

We were surprised to observe no annulation but just a simple acylation, since ketoacid **10** was isolated after work up, essentially as one isomer, with 27% yield (67% corrected yield, based on 60% of recovered ketones). In order to facilitate purification and analysis of compound **10**, it was transformed into β-ketoester **11** in 87% yield by treatment with TMSdiazomethane in acetone. The stereochemistry of compound **11** (three equatorial allyl groups) was deduced by

NMR spectroscopy, and particularly by comparing the high field chemical shifts, (for ^{1}H as well as for ^{13}C NMR), of the axial methyl group with those recorded for the previously obtained triprenyl analogue **13**[13a] (δ_H 0.57 for **11** and 0.56 for **13** and δ_C 15.4 for **11** and 15.1 for **13**). The values for δ_C are attributed to the γ-gauche effect (one equatorial substituent on each side of the *gem*-dimethyl).[20]
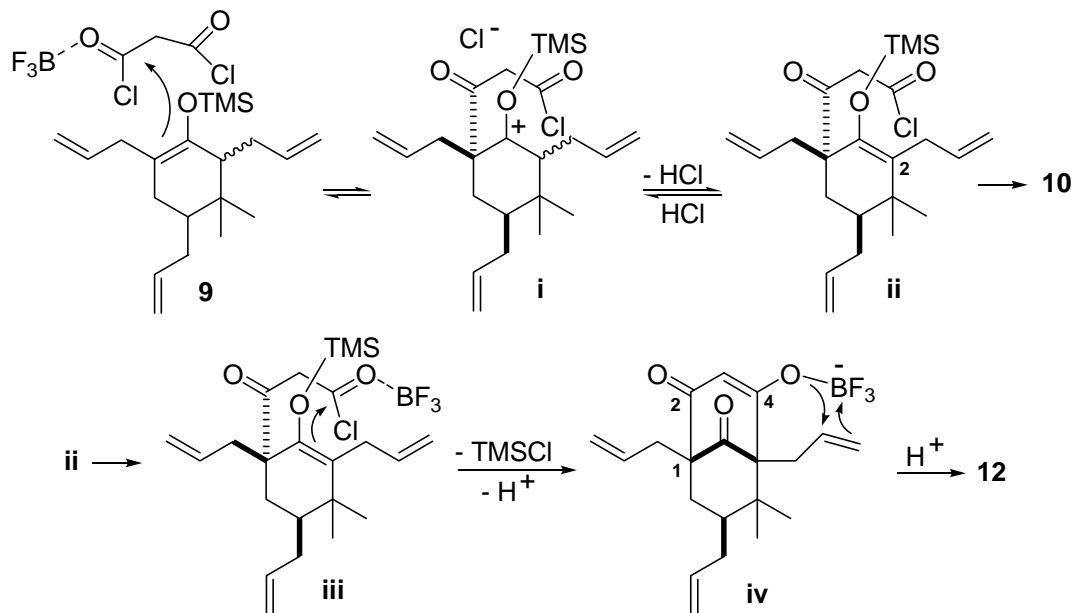
With two equivalents of malonyl dichloride, stoichiometry described by Stoltz in the case of the reaction with a TBS enol ether,[19] and a longer reaction time at room temperature, Effenberger annulation[14] could be achieved, but with concomitant *O*-cyclization. These conditions afforded **10** again (17%) but compound **12** also was isolated as one isomer, with 24% yield (46% corrected yield, based on 48% of recovered ketones). Thus, in a single operation, the tricyclic skeleton of hyperibones H and I was obtained. It should be noted that these natural products, with a 2-hydroxy-2-propyl substituent at C-3 are, to the best of our knowledge, the only PPAPs with the heterocycle adjacent to the *gem*-dimethyl group.[8]

For the tricyclic compound **12**, the furan ring was positioned adjacent to the *gem*-dimethyl group, according to correlations of these CH$_3$ groups with the bridgehead C-1 and of H-2 with C-1 and with the quaternary C-11 observed in the HMBC NMR spectrum (for numbering, see hyperibone I). The carbonyl bridge and the substituent at C-10 were shown to be *cis*, i.e. with the C-10 allyl group equatorial (*exo*). This was deduced, as for PPAPs in general,[1] from the upfield shift of the axial methyl group at C-11 in the ^{13}C NMR spectrum (δ_C 16.0), due to the γ-gauche interaction shielding of this methyl group by the C-10 allyl group.[20] The value of the chemical shift of C-10 (δ_C 39.7) is also in agreement with an equatorial substituent bound to this carbon.[3b] The *cis* relationship of the methyl group at C-3 (on the heterocycle) with the carbonyl bridge was assumed by comparing coupling constants for H-2α and H-2β with those of hyperibones H and I.[8]

Formation of the tetrahydrofuran ring is surprising since the allyl group is much less electron-rich than the prenyl group in the initial series. Moreover, cyclization involving the enolic part of the β-dicarbonyl moiety and the bridgehead substituent adjacent to the *gem*-dimethyl system was unexpected. Such a regioselectivity concerning reactivity of this particular β-diketonic system is not generally observed for inter- or for intramolecular acidic *O*-alkylations.[6, 10a-c, 19] In the case of natural *O*-cyclized type B PPAPs, the heterocycle (usually six-membered) is also generally distal from the *gem*-dimethyl group.[1, 21] However, a compound with a tetrahydropyran adjacent to the quaternary carbon has been obtained as a minor product by radical oxidation of garcinol.[22]

A possible mechanistic pathway, which could explain the formation, as well as the stereochemistry, of **10** and **12**, is shown in Scheme 4. Malonyl dichloride, activated by BF$_3$, might acylate the likely major enol ethers **9**, *anti* to the 4-allyl group (cyclohexanone numbering) to form **i** (attack on the supposed minor isomer is defavored for steric reasons). More generally, alkylation of cyclohexanones enolates possessing a structure analogous to **9** proceeds mostly *anti* to the 4-substituent.[9a, 13a, 23] As the cyclization is difficult (formation of a compound with two contiguous quaternary carbons), slight conformational modifications might prevent the

chlorocarbonyl function of **ii** from reaching the optimal distance (and with a favorable geometry) from C-2. Formation of the ketoacid **10**, with the stereochemistry shown in Scheme 3, after hydrolytic work up, could reflect the difficulty of cyclization from **ii**.

Scheme 4. Tentative mechanistic interpretation.

In the presence of an excess of malonyl dichloride (two equivalents), the rate of formation and the concentration of **i** might be increased, as its generation is probably reversible. Therefore, the amount of **ii** could also be higher, allowing a second acylation, intramolecular this time and possibly via **iii**, as in the prenyl series.[11] In the case of the tricyclic product **12**, formation of an intermediate (**iv**) with BF_3 coordinated to the oxygen bound to C-4 (bicyclo[3.3.1]nonane-2,4,9-trione numbering) might favor the participation of the allyl group close to this oxygen. The ring size is the result of an addition following Markovnikov's rule and the advantage of the allyl group, here, is to afford a five membered heterocycle.
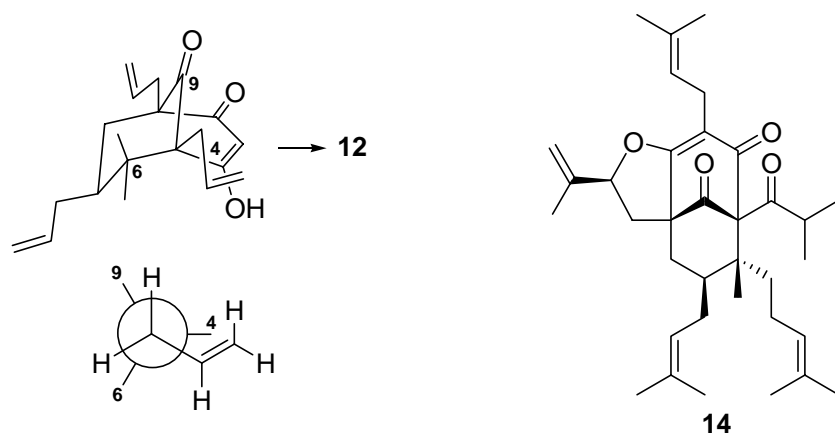
The stereochemistry of **12** at C-3 could be attributed to a geometry, for the allyl group, close to that of its favored conformation,[24] as shown above. It should be noted that the formation of **14**, a product of hyperforine lead tetraacetate oxidation, proceeded with a similar stereochemical outcome (*cis* isopropenyl group and carbonyl bridge).[25]

The less efficient α,α'-annulation in the case of **9**, compared to **1**, and the formation of a tricyclic product only in the case of the allyl substituted derivative remain unclear. However, small differences between allyl and prenyl groups, from steric and conformational points of view, could modify the regioselectivity of TMS enol ethers formation and also affect cyclization processes.

Conclusions

Reaction of 2,4,6-triallyl-3,3-dimethylcyclohexanones TMS enol ethers **9** with malonyl dichloride in the presence of $BF_3 \cdot Et_2O$, was carried out in order to obtain an allyl substituted bicyclo[3.3.1]nonane-2,4,9-trione. Depending on the conditions, formation of the ketoacid **10**, by acylation without cyclization, or of the tricyclic compound **12**, by Effenberger α,α'-annulation with concomitant *O*-cyclization, were observed. Thus, in a simple operation, a product with the same core skeleton than that of hyperibones H and I was obtained.

Experimental Section

General. NMR spectra were recorded with the following Bruker spectrometers: AC250 (250 MHz), AC300 (300 MHz), Avance 300 (300 MHz), DPX 400 (400 MHz) and Avance 500 (500 MHz). FTIR spectra were recorded as a film on NaCl or diamond (SensIR Durasamp*IRII*) cell with a Perkin-Elmer Spectrum BX FT-IR spectrophotometer. Mass spectra were recorded by electrospray ionization with a Micromass LCT (ESI-TOF) spectrometer.

2-Allyl-3-isopropoxycyclohex-2-enone 4. To a solution of **3**[15] (8.58 g, 56.4 mmol) in acetone (112 mL), were added K_2CO_3 (31.0 g, 222.7 mmol) and 2-iodopropane (17 mL, 170.3 mmol). The reaction mixture was refluxed during 64 h and then cooled to room temperature. Evaporation of acetone afforded a residue which was taken up in 200 mL of a 1/1 mixture of water and ether. Aqueous phase was extracted three times with ether, and the combined organic phases were washed with saturated Na_2CO_3, H_2O, brine, dried over Na_2SO_4, and concentrated to give **4** as a pale brown oil (10.8 g, 99%) which was used without any purification. IR 2977, 1644, 1604, 1368, 1238, 1099 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.28 (d, J = 6.2 Hz, 6 H), 1.98 (quint., J = 6.4 Hz, 2 H), 2.35 (t, J = 6.4 Hz, 2 H), 2.54 (t, J = 6.1 Hz, 2 H), 3.02 (d, J = 6.4 Hz, 2 H), 4.54 (hept., J = 6.2 Hz, 1 H), 4.88 (dd, J = 10.1 Hz, 1.8 Hz, 1 H), 4.98 (dd, J = 16.8 Hz, 1.8 Hz, 1 H), 5.77 (ddt, J = 16.8 Hz, 10.1 Hz, 6.4 Hz, 1 H), ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.2, 23.0 (2 C), 25.7, 26.6, 36.6, 70.3, 113.9, 118.7, 136.7, 171.1, 197.9; MS (ESI) 217.1 $C_{12}H_{18}NaO_2$ (M+Na)$^+$.

2,6-Diallyl-3-isopropoxycyclohex-2-enone 5. To a cooled (-78 °C) solution of diisopropylamine (8.6 mL, 61.3 mmol) in THF (72 mL), was added BuLi (1.6 M in hexanes, 35.9 mL, 57.4 mmol) and stirring was continued during 30 min. At the same temperature was added dropwise a solution of **4** (10.8 g, 55.6 mmol) in THF (70 mL) and stirring was continued during 1 h. Then, 97% allyl bromide (6.0 mL, 67.2 mmol) was added dropwise and the reaction mixture was slowly warmed to room temperature overnight. Saturated NH_4Cl and Et_2O were added and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, and evaporated to give **5** as a crude oil (13.05 g) which was used directly in the next step without any further purification. An analytical sample of **5** could be obtained by column chromatography on silica gel (heptane/ethyl acetate: 95/5). IR 2977, 1639, 1610, 1453, 1370, 1237, 1106, 991, 910 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.27 (d, J = 6.2 Hz, 3 H), 1.29 (d, J = 6.2 Hz, 3 H), 1.69 (m, 1 H), 2.09 (m, 2 H), 2.23 (m, 1 H), 2.50-2.62 (m, 3 H), 3.02 (d, J = 6.4 Hz, 2 H), 4.54 (hept., J = 6.2 Hz, 1 H), 4.87 (dd., J = 10.1 Hz, 1.8 Hz, 1 H), 4.98 (dd, J = 17.1 Hz, 1.8 Hz, 1 H), 5.03 (2 dd overlap, J = 17.1 Hz, 10.1 Hz, 1.5 Hz, 2 H), 5.77 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 23.0 (2 C), 24.7, 25.7, 26.9, 34.3, 44.3, 70.1, 113.8, 116.5, 118.1, 136.7 (2 C), 170.3, 198.8; HRMS (ESI) m/z found 257.1511, calcd for $C_{15}H_{22}NaO_2$ (M+Na)$^+$ 257.1517

2,4-Diallyl-3-methylcyclohex-2-enone 6. To a cooled (0 °C) solution of crude **5** (13.05 g, 55.7 mmol) in THF (70 mL), were added dropwise a solution of MeLi (1.6 M in Et$_2$O, 52.0 mL, 83.2 mmol). After addition was completed, stirring was continued for 30 min at room temperature. Then 1 N HCl (139 mL) was carrefully added at 0° C and vigorous stirring was maintained during 30 min. The organic phase was separated and aqueous phase was extracted three times with Et$_2$O. The combined organic phases were dried over Na_2SO_4, filtrated and evaporated. Column chromatography on silica gel (heptane/ethyl acetate: 98/2) afforded **6** as a colorless oil (9.2 g, 87% over two steps). IR 2925, 1660, 1638, 1443, 1377, 994, 908 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.91 (m, 1 H), 1.94 (s, 3 H), 2.02 (m, 1 H), 2.21 (m, 1 H), 2.26 (m, 1 H), 2.34 (m, 1 H), 2.43 (m, 1 H), 2.49 (m, 1 H), 3.04 (d, J = 5.9 Hz, 2 H), 4.92 (m, 2 H), 5.06 (m, 2 H), 5.70 (m, 1 H), 5.77 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.9, 25.3, 29.3, 33.4, 35.6,

40.8, 114.2, 117.0, 133.2, 134.5, 136.4, 159.4, 197.7; HRMS (ESI) *m/z* found 213.1256, calcd for $C_{17}H_{26}NaO$ (M+Na)$^+$ 213.1255.

2,4-Diallyl-3,3-dimethylcyclohexanone 7. To a suspension of CuI (18.2 g, 95.6 mmol) in Et$_2$O (270 mL) at 0 °C, was added dropwise MeLi (1.6 M in Et$_2$O, 56.8 mL, 90.9 mmol). Upon cooling at –78 °C, freshly distilled Et$_2$O•BF$_3$ (11.3 mL, 89.2 mmol) was added dropwise and, after 10 min at this temperature, a solution of **6** (1.7 g, 8.93 mmol) in THF (7.0 mL) was added. The reaction was stirred for 3 h 30 at –78 °C and quenched by addition of 380 mL of a 9/1 solution of saturated NH$_4$Cl and 25% aqueous ammonia. The temperature was allowed to increase and stirring was continued under normal atmosphere until the mixture turned deep blue. The suspension was filtered through celite, the organic layer separated, and the aqueous layer extracted with Et$_2$O. The combined organic phases were dried over Na$_2$SO$_4$, and briefly purified on silica gel to give a colorless oil as a mixture of two epimers (4/3) (1.55 g, 83%). IR 2970, 2935, 2869, 1711, 1639, 1432, 1371, 997, 908 cm^{-1}; HRMS (ESI) *m/z* found 229.1569 calcd for $C_{14}H_{22}NaO$ (M+Na)$^+$ 229.1568. Analytical samples of **7c** and **7t** were obtained by column chromatography on silica gel (heptane/ethyl acetate: 99/1).

(2S*,4R*)2,4-Diallyl-3,3-dimethylcyclohexanone 7c. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.58 (s, 3 H), 1.10 (s, 3 H), 1.40 (m, 1 H), 1.61 (m, 1 H), 1.66 (m, 1 H), 1.99 (m, 1 H), 2.07 (m, 1 H), 2.24 (dd, *J* = 9.8 Hz, 2.3 Hz, 1 H), 2.29 (m, 1 H), 2.32 (m, 1 H), 2.39 (m, 1 H), 2.53 (m, 1 H), 4.91 (m, 2 H), 5.00 (m, 2 H), 5.71 (m, 1 H), 5.78 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 15.3, 26.7, 27.4, 28.8, 34.7, 42.1, 43.2, 46.9, 61.0, 114.9, 116.0, 137.8, 138.4, 211.5.

(2R*,4R*)2,4-Diallyl-3,3-dimethylcyclohexanone 7t. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (s, 3 H), 0.96 (s, 3 H), 1.53 (m, 1 H), 1.69 (m, 1 H), 1.84 (m, 1 H), 1.97 (m, 1 H), 2.13 (dd, *J* = 11.1 Hz, 4.1 Hz, 1 H), 2.23 (m, 1 H), 2.25 (m, 1 H), 2.28 (m, 1 H), 2.33 (m, 1 H)), 2.39 (m, 1 H), 4.96 (m, 2 H), 5.03 (m, 2 H), 5.64 (m, 1 H), 5.78 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 23.5, 25.8, 26.8, 30.8, 33.5, 37.8, 40.2, 41.1; 61.2, 115.9, 116.1, 136.2, 137.8, 213.8.

2,4,6-Triallyl-3,3-dimethylcyclohexanone 8. To a cooled (0 °C) solution of diisopropylamine (4.2 mL, 29.9 mmol) in THF (10.7 mL), was added BuLi (2.0 M in hexanes, 13.8 mL, 27.6 mmol) and stirring was continued during 30 min at the same temperature. The solution was cooled at –78 °C and a solution of the mixture of **7c** + **7t** (4.75 g, 23.0 mmol) in THF (4.6 mL) was added dropwise. Stirring was continued during 1 h at the same temperature. Then, a solution of 97% allyl bromide (2.7 mL, 30.3 mmol) in HMPA (15.0. mL, 86.2 mmol) was added dropwise and the mixture was slowly warmed to room temperature overnight. Saturated NH$_4$Cl and Et$_2$O were added and the aqueous phase was extracted twice with Et$_2$O. The combined organic phases were dried over Na$_2$SO$_4$, filtrated and evaporated. Column chromatography on silica gel (heptane/ethyl acetate: 99/1) gave **8** as a 2/3 β/α mixture (4.4 g, 78%). IR 2971, 1707, 1639, 1435, 1390, 1370, 994, 908 cm^{-1}; HRMS (ESI) *m/z* found 269.1881, calcd for $C_{17}H_{26}NaO$ (M+Na)$^+$ 269.1881. Analytical samples of **8β** and **8α** were obtained by column chromatography on silica gel (heptane/ethyl acetate: 100/0.9).

(2S*,4S*,6S*)-2,4,6-triallyl-3,3-dimethylcyclohexanone 8β. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.63 (s, 3 H), 1.13 (s, 3 H), 1.56 (m, 1 H), 1.69 (m, 1 H), 1.82 (m, 1 H), 1.93 (m, 1 H), 2.02

(m, 1 H), 2.28 (m, 1 H), 2.42 (m, 2 H), 2.45 (m, 2 H), 2.55 (m, 1 H), 4.92 (m, 2 H), 4.99 (m, 2 H), 5.03 (m, 2 H), 5.61 (m, 1 H), 5.73 (m, 1 H), 5.78 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 15.5, 26.9, 27.4, 32.4, 34.6, 36.1, 41.8, 43.4, 49.6, 57.3, 115.0, 116.1, 117.0, 135.0, 137.8, 138.4, 214.2.

(2R*,4S*,6S*)-2,4,6-triallyl-3,3-dimethylcyclohexanone 8α. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.81 (s, 3 H), 1.08 (s, 3 H), 1.45 (m, 1 H), 1.55 (m, 1 H), 1.90 (m, 2 H), 2.00 (m, 1 H), 2.27 (m, 2 H), 2.38 (m, 1 H), 2.42 (m, 1 H), 2.50 (m, 1 H), 2.52 (m, 1 H), 4.96 (m, 2 H), 5.00 (m, 2 H), 5.07 (m, 2 H), 5.70 (m, 1 H), 5.77 (m, 1 H), 5.80 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 24.2, 26.8, 27.5, 31.4, 32.5, 33.4, 42.9, 44.8, 44.9, 56.2, 115.1, 116.1, 116.2, 136.4, 137.8, 138.4, 212.1.

2,4,6-Triallyl-3,3-dimethylcyclohexanone trimethylsilyl enol ethers 9. To a cooled (0 °C) solution of a mixture of cyclohexanones **8** (1 g, 4.06 mmol) in CH$_2$Cl$_2$ (7.0 mL) was added freshly distilled Et$_3$N (1.13 mL, 8.12 mmol). The reaction mixture was stirred during 15 min and TMSOTf (1.1 mL, 6.08 mmol) was added dropwise. The solution was slowly warmed to room temperature and stirred overnight. Pentane was added and the two layers were separated. The pentane phase was washed with satured NH$_4$Cl and with brine. The organic phase was dried over Na$_2$SO$_4$, and concentrated to a colorless oil which was used without further purification in the next step. **9** was obtained quantitatively as a mixture of 3 isomers. The proportion of each isomer could not be determined by NMR spectroscopy.

Methyl 3-oxo-3-((1R*,3S*,5S*)-1,3,5-triallyl-4,4-dimethyl-2-oxocyclohexyl)propanoate 11. To a cooled (-10 °C) solution of silyl enol ethers **9** (570 mg, 1.79 mmol) in CH$_2$Cl$_2$ (9 mL) were successively added dropwise redistilled Et$_2$O•BF$_3$ (68 µL, 0.54 mmol) and freshly distilled malonyl dichloride 184 µL, 1.88 mmol). The reaction mixture was stirred during 2 h, warmed to room temperature during 2 h, quenched by DMAP (773 mg, 6.27 mmol) and stirred during 15 min. The solution was diluted by Et$_2$O and hydrolysed by 1 N HCl. The layers were separated and the aqueous phase was extracted 3 times by Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated to a yellow oil. Purification by flash chromatography (CH$_2$Cl$_2$/MeOH: 95/5) gave **10** (160 mg, 27%) as a yellow oil and a 1/1 mixture of ketones (356 mg, 60%) as a colorless oil. To a solution of ketoacid **10** (100 mg, 0.30 mmol) in acetone (0.2 mL) at room temperature under an argon atmosphere, was added dropwise TMSdiazomethane (2 M in hexanes, 250 µL, 0.5 mmol) and the reaction mixture was stirred for 4 h. It was directly evaporated and purified by flash chromatography (heptane/ethyl acetate: 95/5) to afford 91 mg (87%) of keto ester **11** as a colorless oil. IR 2973, 1753, 1699, 1440, 1436, 995, 913 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.57 (s, 3 H), 1.08 (s, 3 H), 1.13 (m, 1 H), 1.64 (m, 1 H), 1.83 (m, 1 H), 2.06 (m, 1 H), 2.21 (dd, J = 10.1 Hz, 2.4 Hz, 1 H), 2.34 (m, 1 H), 2.35 (m, 1 H), 2.39 (m, 1 H), 2.57 (m, 1 H), 2.60 (m, 1 H), 3.17 (d, J = 16.3 Hz, 1 H), 3.38 (d, J = 16.3 Hz, 1 H), 3.71 (s, 3 H), 4.97 (m, 2 H), 5.05 (m, 2 H), 5.09 (m, 2 H), 5.57 (m, 1 H), 5.72 (m, 1 H), 5.82 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 15.4, 26.4, 27.5, 34.6, 35.6, 38.4, 42.9, 45.3, 52.4, 59.3, 61.9, 67.6, 116.3, 116.4, 119.3, 131.8, 137.0, 137.3, 167.0, 199.8, 207.8; HRMS (ESI) m/z found 369.2042, calcd for C$_{21}$H$_{30}$NaO$_4$ (M+Na)$^+$ 369.2042.

(1R*,3R*,8S*,10R*)-8,10-Diallyl-3,11,11-trimethyl-4-oxa-tricyclo[6.3.1.0^{1,5}]dode-5-ene-7,12-dione 12. To a cooled (-10 °C) solution of silyl enol ethers **9** (503 mg, 1.58 mmol) in CH_2Cl_2 (8 mL) were successively added dropwise redistillated $Et_2O \bullet BF_3$ (59 μL, 0.47 mmol) and freshly distilled malonyl dichloride (310 μL, 3.18 mmol). The reaction mixture was stirred during 2 h, warmed to room temperature during 18 h, quenched by DMAP (543 mg, 4.40 mmol) and stirred during 15 min. The solution was diluted by Et_2O and hydrolysed by 1 N HCl. The layers were separated and the aqueous phase was extracted 3 times by Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated to a yellow oil. Purification by flash chromatography (CH_2Cl_2/MeOH: 96/4) gave **12** (90 mg, 17%) as a yellow oil, **10** (120 mg, 24%) as a colorless oil and a 5/6 mixture of ketones (250 mg, 48%) as a colorless oil. **12**: IR 2976, 1727, 1626, 1377, 1193, 995, 912 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.73 (s, 3 H), 0.99 (s, 3 H), 1.39 (m, 1 H), 1.52 (d, J = 6.4 Hz, 3 H), 1.65 (m, 1 H), 1.71 (dd, J = 14.0 Hz, 6.9 Hz, 1 H), 1.89 (m, 1 H), 2.00 (dd, J = 13.3 Hz, 4.2 Hz, 1 H), 2.29 (m, 1 H), 2.50 (dd overlap, J = 7.8 Hz, 6.9 Hz, 2 H), 3.06 (dd, J = 14.0 Hz, 9.7 Hz, 1 H), 4.50 (m, 1 H), 5.00 (m, 2 H), 5.05 (m, 2 H), 5.62 (m, 1 H), 5.66 (m, 1 H), 5.86 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.0, 20.2, 23.7, 30.0, 35.3 (2 C), 39.7, 40.3, 45.3, 62.0, 69.3, 81.6, 107.1, 117.0, 118.0, 134.0, 136.5, 177.6, 197.3, 205.5; HRMS (ESI) m/z found 337.1777, calcd for $C_{20}H_{26}NaO_3$ (M+Na)$^+$ 337.1780.

Acknowledgements

References and Notes

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